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on behalf of the Dutch POPS-19 Collaborative Study Group

Preterm birth and later insulin resistance: effects of birth weight and postnatal growth in a population based longitudinal study from birth into adult life

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Abstract *Aims/hypothesis:* An increased risk of type 2 diabetes mellitus is associated with low birthweight after full-term gestation, including amplification of this risk by weight gain during infancy and adult body composition. Premature birth is also associated with insulin resistance, but studies conducted so far have not provided follow-up into adulthood. We studied the effects of (1) lower birthweight (as standard deviation score [SDS]) and infancy weight gain on insulin resistance in 19-year-olds born before 32 weeks of gestation, and (2) the interaction be-

tween lower birthweight SDS and infancy weight gain, as well as between lower birthweight and adult body composition, on insulin resistance. *Methods:* This was a prospective follow-up study in 346 subjects from the Project on Preterm and Small-for-gestational-age infants cohort, in whom fasting glucose, insulin and C-peptide levels were measured at 19 years. Insulin resistance was calculated with homeostatic modelling (homeostatic model assessment for insulin resistance index [HOMA-IR]). *Results:* Birthweight SDS was unrelated to the outcomes. Rapid infancy weight gain until 3 months post-term was weakly associated with higher insulin level ($p=0.05$). Adult fatness was positively associated with insulin and C-peptide levels and HOMA-IR (all $p<0.001$). On these parameters, there was a statistical interaction between birthweight SDS and adult fat mass ($p=0.002$ to 0.03). *Conclusions/interpretation:* In subjects born very preterm, rapid infancy weight gain until 3 months predicted higher insulin levels at 19 years, but the association was weak. Adult obesity strongly predicted higher insulin and C-peptide levels as well as HOMA-IR. The effect of adult fat mass on these parameters was dependent on its interaction with birthweight SDS.

For a list of participants in the Dutch POPS-19 Collaborative Study Group, see Appendix

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Abbreviations HOMA-IR: homeostatic model assessment for insulin resistance index · POPS: Project on Preterm and Small-for-gestational-age infants · SDS: standard deviation score · SGA: small-for-gestational-age

Introduction

Effects of intrauterine and postnatal growth on the risk, in the general population, of developing type 2 diabetes mellitus are well described. Low birthweight after full-term gestation is associated with insulin resistance, glucose intolerance and type 2 diabetes in later life [1, 2]. The effect of low birthweight on increased type 2 diabetes risk is stronger in subjects who catch up in weight during infancy,

and in those who become overweight during childhood and in adult life [3–5]. Also, low weight in infancy has been associated with type 2 diabetes [1, 6].

Less is known about the effects of intrauterine and postnatal growth on insulin resistance in the growing population of survivors of preterm birth. Recently, it was found that 7-year-old children born prematurely were more insulin-resistant than age-matched normal controls [7]. The effect of prematurity was irrespective of intrauterine growth, although another study in 6-year-old preterm offspring found higher basal insulin and C-peptide levels in subjects with birthweights below the 10th percentile [8]. However, both studies were performed in small populations. Very preterm (i.e. <32 weeks of gestation) infants differ from full-term children in postnatal growth pattern, which is characterised by an initial slowing of growth followed by late catch-up growth [9, 10]. To date, one study has focused on insulin resistance in relation to postnatal weight gain after preterm birth [11]. The investigators found that insulin split products were higher in subjects aged 13–16 years with rapid weight gain in the first 2 weeks postnatally. As these three studies were conducted in paediatric populations, it remains uncertain whether the observed associations in childhood persist into adult life. For the same reason, it is unknown whether there is interaction between low birthweight and adult body composition on insulin resistance after very preterm birth.

We provide here a prospective long-term follow-up into adulthood of a well-described cohort of men and women born very preterm, in whom insulin resistance was assessed at the age of 19 years. Within this study population, we

tested the effects of lower birthweight for gestational age and rapid infancy weight gain on insulin resistance at the age of 19 years. We also tested whether there was interaction between lower birthweight and rapid infancy weight gain, and between lower birthweight and adult body composition, on insulin resistance.

Subjects and methods

Subjects

The Project on Preterm and Small-for gestational-age infants (POPS) study is a nationwide multicentre prospective follow-up study, which comprises 94% of all liveborn very preterm (<32 weeks of gestation) and/or very low birthweight (<1,500 g) infants born in the Netherlands in 1983, and has documented birth, growth and a number of other characteristics from birth onwards [12, 13]. At follow-up visits at age 3 months and 1 year post-term, weight was recorded. At age 19 years, all 637 alive subjects born with a gestational age below 32 weeks who were free from congenital skeletal deformations, Down's syndrome, chromosomal abnormalities, multiple congenital deformations or inborn errors of metabolism, and who were not born to mothers with gestational diabetes, were approached by mail to participate in the POPS-19 study. Subjects with diabetes mellitus, or on thyroid hormone or systemic corticosteroids, as well as pregnant women, were excluded. The approval of the medical ethical committees of all participating centres was obtained for the POPS-19 study.

Table 1 Perinatal characteristics of participants and non-respondents

	Participants	Non-respondents	<i>p</i> value
Number	346	242	
General characteristics			
Males (%)	47.4	66.1	<0.001
Whites (%)	88.3	80.1	0.006
Socio-economic status (1–6)	3.5±1.6	2.8±1.5	<0.001 ^a
Obstetric characteristics			
Maternal age (years)	26.9±5.7	26.4±5.3	0.23
Parity >0 (%)	46.7	50.6	0.35
Part of multiple pregnancy (%)	24.3	21.5	0.43
Hypertension during pregnancy (%)	16.5	15.3	0.70
Smoking during pregnancy (%)	30.0	31.8	0.67
Drugs and alcohol intoxication (%) ^b	50.9	51.2	0.93
Prolonged rupture of membranes (%)	24.0	24.4	0.91
Neonatal characteristics			
Gestational age (weeks)	29.8±1.5	29.8±1.5	0.55
Birthweight			
g	1,332±333	1,354±278	0.39
SDS	−0.09±1.02	−0.08±0.90	0.98
Weight at 3 months post-term			
g	5,169±871	5,234±896	0.40
SDS	−0.92±1.32	−0.94±1.42	0.88
Weight at 1 year post-term			
g	8,909±119	9,084±140	0.14
SDS	−1.00±1.15	−0.95±1.38	0.61

Continuous variables were compared with the independent sample *t*-test. Dichotomous variables were compared by the χ^2 -test

^aMann–Whitney *U*-test

^bSmoking, drinking alcohol, or using soft drugs, hard drugs or methadone during pregnancy

Study protocol

Subjects, who gave written informed consent to participate, were seen after an overnight fast between 08.30 and 10.00 hours between April 2002 and May 2003 at one of the outpatient clinics of the ten participating centres. Assessors were blinded with respect to the perinatal characteristics of the subjects.

Venous blood was obtained after 30 min in a supine position. Thereafter, anthropometry was performed, for which assessors had received extensive training prior to the study, and re-training during the entire study period at 2-month intervals. Subjects were measured barefoot while wearing underclothing only. Weight was measured to the nearest 0.1 kg on a balance scale, and height to the nearest 0.1 cm with a fixed stadiometer. Waist and hip circumferences were measured at 0.1-cm accuracy using standard methods [14]. Four skinfold thickness measurements were taken in duplicate with a calibrated skinfold calliper on the left side of the body: at triceps, biceps, subscapular and iliacal regions. From these measurements, fat mass and the corresponding fat-free mass were calculated using the equations of Durnin and Rahaman [15]. A more detailed description of skinfold thickness measurements obtained in the POPS-19 study has been published elsewhere [16].

Laboratory analyses

Blood samples were stored at -80°C , and thawed only once immediately before analysis. Glucose was measured in a

fully automated computerised laboratory system with an Hitachi 747 (Hitachi, Tokyo, Japan) chemistry analyser, and insulin and C-peptide were measured with highly sensitive RIAs (Linco, St Charles, MO, USA; detection levels 0.1 mU/l and 0.03 mmol/l, respectively; interassay CV 4.7–12.2% and 3.2–9.3% at different levels, respectively). A homeostatic model assessment for insulin resistance index (HOMA-IR) was calculated [17]. Insulin and C-peptide levels, and HOMA-IR were considered as parameters of insulin resistance. Insulin level and HOMA-IR correlate strongly with S_i assessed by the frequently sampled IVGTT in young persons [18, 19].

Statistical analysis

Auxological data at birth and on subsequent occasions were converted to standard deviation scores (SDSs), to correct for (gestational) age and sex, using Swedish references for preterm infants [20], and recently collected Dutch references [14, 21, 22], respectively.

Results in Tables 1 and 2 are presented as means $\pm$ SD, or medians (interquartile range) if variables were not normally distributed (insulin and HOMA-IR). These variables were log-transformed before statistical comparison.

Birthweight is a strong predictor of postnatal size. Therefore, the multivariate linear regression model developed by Li et al. was used to distinguish between the separate effects of birthweight SDS, and of postnatal size (at the age of 3 months, 1 year and 19 years) on the parameters of insulin resistance [23]. First, the effect of birthweight

Table 2 Characteristics of participants at age 19 years by sex

	Men	Women	<i>p</i> value
Number	164	182	
Height			
cm	179.4 $\pm$ 7.7	166.4 $\pm$ 7.3	<0.001
SDS	−0.54 $\pm$ 1.08	−0.60 $\pm$ 1.13	0.66
Weight			
kg	69.1 $\pm$ 10.7	60.2 $\pm$ 10.7	<0.001
SDS	−0.47 $\pm$ 1.12	−0.50 $\pm$ 1.39	0.83
BMI			
kg/m ²	21.4 $\pm$ 2.8	21.7 $\pm$ 3.2	0.44
SDS	−0.17 $\pm$ 1.10	−0.19 $\pm$ 1.24	0.86
Waist circumference			
cm	79.8 $\pm$ 7.9	76.8 $\pm$ 8.7	0.001
SDS	0.19 $\pm$ 1.04	0.70 $\pm$ 0.98	<0.001
WHR			
cm/cm	0.87 $\pm$ 0.06	0.82 $\pm$ 0.08	<0.001
SDS	0.70 $\pm$ 0.92	0.86 $\pm$ 0.97	0.12
Absolute fat mass (kg) ^a	11.1 $\pm$ 5.2	18.2 $\pm$ 6.6	<0.001
Fat-free mass (kg) ^a	57.9 $\pm$ 7.3	42.1 $\pm$ 6.6	<0.001
Fat percentage (%) ^a	15.7 $\pm$ 5.3	29.5 $\pm$ 7.1	<0.001
Glucose (mmol/l)	5.2 $\pm$ 0.4	4.8 $\pm$ 0.4	<0.001
Insulin (mU/l) ^b	8 (6; 11)	8 (7; 11)	0.42
C-peptide (mmol/l)	0.66 $\pm$ 0.23	0.69 $\pm$ 0.21	0.16
HOMA-IR ^b	1.9 (1.4; 2.6)	1.8 (1.4; 2.3)	0.46

^aNo population reference values available

^bMedian (interquartile range)

Table 3 Regression analyses of birthweight SDS and infancy weight gain on the parameters of insulin resistance at age 19 years

	Crude ^a			Adjusted ^b			Interaction with birthweight SDS		
	<i>n</i>	<i>B</i> (95% CI)	<i>p</i> value	<i>n</i>	<i>B</i> (95% CI)	<i>p</i> value	<i>n</i>	<i>B</i> (95% CI)	<i>p</i> value
Log insulin									
Birthweight SDS	346	−0.006 (−0.025; 0.012)	0.49	339	−0.002 (−0.024; 0.020)	0.86	—	—	—
Weight SDS at 3 months	321	0.017 (0.001; 0.033)	0.04	315	0.018 (0; 0.036)	0.05	321	−0.015 (−0.034; 0.03)	0.10
Weight SDS at 1 year	317	0.016 (−0.002; 0.035)	0.08	313	0.014 (−0.005; 0.033)	0.15	317	−0.006 (−0.025; 0.013)	0.53
C-peptide									
Birthweight SDS	346	−0.020 (−0.043; 0.002)	0.08	339	−0.020 (−0.043; 0.003)	0.08	—	—	—
Weight SDS at 3 months	321	−0.010 (−0.030; 0.011)	0.36	315	−0.006 (−0.029; 0.017)	0.61	321	0.011 (−0.012; 0.035)	0.34
Weight SDS at 1 year	317	−0.003 (−0.026; 0.019)	0.78	313	−0.003 (−0.027; 0.021)	0.81	317	0.004 (−0.018; 0.027)	0.70
Log HOMA-IR									
Birthweight SDS	345	−0.005 (−0.025; 0.015)	0.65	338	0 (−0.23; 0.23)	1.00	—	—	—
Weight SDS at 3 months	320	0.017 (0; 0.035)	0.05	314	0.017 (−0.003; 0.036)	0.09	320	−0.011 (−0.031; 0.009)	0.27
Weight SDS at 1 year	316	0.020 (0; 0.040)	0.05	312	0.017 (−0.004; 0.037)	0.12	316	−0.003 (−0.023; 0.017)	0.79

^aAdjusted only for sex^bAdjusted for sex, race (white or non-white), socio-economic status ($\leq$ or >2), multiple pregnancy (singleton or non-singleton), gestational age ($\leq$ or >30 weeks), parity (0 or >0), and hypertension during pregnancy (yes or no)

SDS on the parameters of insulin resistance was studied. Subsequently, residual (observed–expected) postnatal size was entered into the model. Expected postnatal size was based upon birthweight SDS only. Hence, residual postnatal size can be interpreted as growing more (or less) than would be expected from a given birthweight SDS.

Thereafter, the interaction term (birthweight SDS $\times$ residual, with subtraction of means) was entered. Recently [24], the algebraic concept of this model was explained, showing that it can be rewritten to the model by Lucas et al. [25] In the applied model, postnatal size is made statistically unrelated to birthweight SDS.

Table 4 Regression analyses of adult size and body composition on the parameters of insulin resistance at age 19 years

	Crude ^a			Adjusted ^b			Interaction with birthweight SDS		
	<i>n</i>	<i>B</i> (95% CI)	<i>p</i> value	<i>n</i>	<i>B</i> (95% CI)	<i>p</i> value	<i>n</i>	<i>B</i> (95% CI)	<i>p</i> value
Log insulin									
Height SDS	339	0.004 (−0.015; 0.022)	0.70	333	0.001 (−0.018; 0.020)	0.93	339	−0.022 (−0.040; −0.005)	0.01
BMI SDS	338	0.060 (0.045; 0.075)	<0.001	332	0.057 (0.042; 0.072)	<0.001	338	−0.012 (−0.026; 0.002)	0.09
Waist circumference SDS	341	0.076 (0.059; 0.093)	<0.001	335	0.073 (0.056; 0.091)	<0.001	341	−0.016 (−0.032; 0)	0.06
WHR SDS	340	0.030 (0.010; 0.049)	0.003	334	0.045 (0.023; 0.066)	<0.001	340	−0.007 (−0.026; 0.012)	0.48
Absolute fat mass (kg)	335	0.011 (0.008; 0.014)	<0.001	329	0.011 (0.008; 0.014)	<0.001	335	−0.005 (−0.009; −0.002)	0.003
Fat percentage (%)	337	0.008 (0.005; 0.011)	<0.001	331	0.009 (0.006; 0.012)	<0.001	337	−0.004 (−0.007; 0)	0.03
C-peptide									
Height SDS	339	0.016 (−0.007; 0.038)	0.18	333	0.011 (−0.012; 0.035)	0.34	339	0.001 (−0.020; 0.022)	0.92
BMI SDS	338	0.056 (0.037; 0.075)	<0.001	332	0.055 (0.035; 0.074)	<0.001	338	−0.017 (−0.035; 0.001)	0.06
Waist circumference SDS	341	0.084 (0.063; 0.106)	<0.001	335	0.083 (0.061; 0.105)	<0.001	341	−0.012 (−0.032; 0.008)	0.25
WHR SDS	340	0.045 (0.021; 0.069)	<0.001	334	0.056 (0.030; 0.082)	<0.001	340	−0.019 (−0.042; 0.004)	0.11
Absolute fat mass (kg)	335	0.016 (0.012; 0.019)	<0.001	329	0.016 (0.012; 0.019)	<0.001	335	−0.006 (−0.010; −0.002)	0.006
Fat percentage (%)	337	0.013 (0.010; 0.017)	<0.001	331	0.014 (0.010; 0.017)	<0.001	337	−0.004 (−0.008; 0)	0.03
Log HOMA-IR									
Height SDS	338	0.004 (−0.016; 0.024)	0.70	332	0.001 (−0.020; 0.021)	0.93	338	−0.023 (−0.042; −0.004)	0.02
BMI SDS	337	0.065 (0.050; 0.081)	<0.001	331	0.063 (0.047; 0.079)	<0.001	337	−0.013 (−0.028; 0.002)	0.09
Waist circumference SDS	340	0.083 (0.065; 0.101)	<0.001	334	0.081 (0.062; 0.099)	<0.001	340	−0.019 (−0.036; −0.001)	0.04
WHR SDS	339	0.034 (0.013; 0.055)	0.002	333	0.047 (0.024; 0.070)	<0.001	339	−0.007 (−0.028; 0.014)	0.50
Absolute fat mass (kg)	334	0.012 (0.009; 0.015)	<0.001	328	0.013 (0.010; 0.016)	<0.001	334	−0.006 (−0.009; −0.002)	0.002
Fat percentage (%)	336	0.009 (0.006; 0.012)	<0.001	330	0.010 (0.007; 0.013)	<0.001	336	−0.004 (−0.008; −0.001)	0.01

^aAdjusted only for sex^bAdjusted for sex, race (white or non-white), and socio-economic status ($\leq$ or >2)

Analyses with birthweight SDS and infancy weight gain were repeated with adjustment for the possible confounders sex, race (white or non-white), socio-economic status ($\leq$ or >2), multiple pregnancy (singleton or non-singleton), gestational age ($\leq$ or >30 weeks), parity (0 or >0) and hypertension during pregnancy (yes or no). Analyses with adult size and body composition were repeated with adjustment for sex, race and socio-economic status.

Statistical significance was defined as a p value ≤ 0.05 . Non-linear associations were tested by first producing quarters of birthweight SDS and infancy weight gain. These quarters were compared with respect to the parameters of insulin resistance.

Results

At age 19 years, 637 men and women born before 32 weeks of gestation were still alive and eligible for inclusion: 395 consented to participate, whereas 242 refused or were not traceable. Three of the 395 participants met one of the exclusion criteria (one woman was pregnant at the time of assessment, and two subjects used systemic corticosteroids), 27 failed to give blood, and 19 attended not-fasted. Therefore, 346 individuals were included in the statistical analyses.

Non-response was associated with male sex, non-white race and lower socio-economic status (Table 1). It was not associated with gestational age or birthweight. Nineteen individuals (6%) had a birthweight below -2 SDS, 73 (23%) had a weight at 3 months below -2 SDS, and 57 (18%) had a weight at 1 year below -2 SDS.

For both sexes, mean values for height and weight were below the population reference means, while the means for waist circumference and WHR were greater, especially in the women (Table 2). Women had greater absolute and relative fat mass than men. Men had greater fat-free mass and higher glucose levels than women. There was no difference between the sexes for insulin and C-peptide levels and HOMA-IR. Of the women, 121 (67%) used oral contraceptives at the time of assessment, but there were no significant differences in the parameters of insulin resistance between pill and non-pill users (data not shown).

Birthweight SDS was unrelated to the parameters of insulin resistance (Table 3). Rapid infancy weight gain until 3 months was associated with a higher insulin level and HOMA-IR. After correction for possible confounders, the strength of the relationship with HOMA-IR remained unchanged but statistical significance was lost. Rapid infancy weight gain until 1 year was associated only with higher HOMA-IR, which relationship lost statistical significance after correction for possible confounders. No interaction between birthweight SDS and infancy weight gain on the parameters of insulin resistance was observed. There was no evidence for non-linearity in the associations between early growth and the parameters of insulin resistance (data not shown).

Fig. 1 Effects of birthweight SDS and adult absolute fat mass on log HOMA-IR at age 19 years. *LBW* lower birthweight SDS; *HBW* higher birthweight SDS. *HBW-lean* birthweight SDS ≥ 0 and absolute fat mass $\leq$ median for sex ($n=78$); *LBW-lean* birthweight SDS < 0 and absolute fat mass $\leq$ median for sex ($n=90$); *HBW-obese* birthweight SDS ≥ 0 and absolute fat mass $>$ median for sex ($n=85$); *LBW-obese* birthweight SDS < 0 and absolute fat mass $>$ median for sex ($n=81$)

Except for height SDS, all measures of adult size and body composition were strongly associated with insulin and C-peptide levels as well as HOMA-IR (Table 4). Interaction between birthweight SDS and adult absolute and relative fat mass on these parameters was observed. Also, interaction between birthweight SDS and adult height SDS on insulin level and HOMA-IR, and between birthweight SDS and adult waist circumference SDS on HOMA-IR, was found. Fig. 1 displays the direction of the interaction of birthweight SDS and adult absolute fat mass on HOMA-IR, showing that higher fat mass after lower birthweight SDS has larger effects on the parameters of insulin resistance than does higher fat mass after higher birthweight SDS.

Discussion

From birth onwards we followed a relatively large cohort of subjects born very preterm. At age 19 years, insulin resistance was assessed using fasting levels of insulin and C-peptide as well as HOMA-IR. We found that rapid infancy weight gain until 3 months predicted higher insulin levels at age 19 years, but the association was weak. Adult fat accumulation strongly predicted higher insulin and C-peptide levels as well as higher HOMA-IR at age 19 years. The effect of adult fat accumulation on these parameters of insulin resistance was dependent on its interaction with birthweight SDS. This was most clearly the case for increased fat mass per se, rather than for more abdominal fat. However, it should be emphasised that the typical centralisation of fat distribution occurs with advancing age so that such relationships may become more clear later in adulthood.

It has been suggested that the association between early growth and type 2 diabetes risk is the result of a biological phenomenon which has been called fetal or perinatal programming [26]. Throughout the years, several hypotheses based on the concept of programming have been proposed to underlie this association, including the thrifty phenotype, fetal salvage, catch-up growth and stem-cell hypotheses [27–30]. There are also indications that the association is not the result of programming but of confounding (especially by socio-economic status), selective survival or response [31, 32], or genes that affect both the path of early growth and insulin resistance [33]. Despite incomplete follow-up, our participants did not significantly differ from non-respondents in perinatal characteristics. Non-response was higher among men, non-whites and those with lower socio-economic status. As expected, we found that subjects with lower socio-economic status had higher parameters of insulin resistance than those with higher socio-economic status, but the difference was not statistically significant. We also found that whites were as equally insulin resistant as the rather heterogeneous group of non-whites, including 11 subjects of Mediterranean origin, ten Africans, 15 Asians and four others (data not shown), while it is known that prevalence rates of type 2 diabetes are substantially higher among blacks and Indians. The question arises whether selective response could account for (part of) the observed associations in our study sample. Statistical adjustment for a number of variables, including socio-economic status and race, in regression analyses hardly changed any of the coefficients between early growth and the parameters of insulin resistance. This makes bias introduced by selective response less likely, although it does not exclude the possibility completely. A possible relationship between birthweight SDS and the parameters of insulin resistance would be concealed if the low birthweight SDS subjects with a high risk of insulin resistance selectively declined to participate. Furthermore, the relationship between infancy weight gain and insulin level would be artificial if the slow weight gain subjects with a high risk of insulin resistance selectively refused to participate. This seems not very likely. Moreover, although non-response was associated with demographic factors linked to insulin resistance, in the entire birth cohort ($n=1,012$) there were no effects of race or socio-economic status on birthweight SDS or infancy weight gain.

Although the majority of full-term small-for-gestational-age (SGA) babies show catch-up growth after birth [34], infancy weight gain of our study population was slow, which is reflected by the low mean weight SDS at 3 months and 1 year. However, in contrast to full-term SGA babies, many very preterm infants suffer from life-threatening conditions after birth which require a shift in energy expenditure, enabling them to survive at the expense of somatic growth; e.g. by respiratory distress necessitating assisted ventilation, or infections.

To date, a number of studies have investigated the effect of infancy weight gain on later type 2 diabetes [3, 11, 35,

36]. In middle-aged subjects, low weight at birth and at age 1 year were associated with type 2 diabetes, but the rate of weight gain in the first year of life was unrelated to type 2 diabetes [35]. However, in 1-year-old infants born SGA, catch-up growth in weight until age 1 year was associated with higher fasting insulin levels [3]. Similarly, in children aged 8 years, rapid weight gain between birth and age 3 years was related to insulin resistance [36]. Also in prematurely born subjects aged 13–16 years, effects of early postnatal weight gain on later insulin resistance have been reported. Boys and girls with rapid weight gain in the first 2 weeks postnatally had higher concentrations of proinsulin and 32–33 split proinsulin [11]. Our findings in young adults born very preterm support these previous observations in paediatric populations.

We found that lower birthweight SDS strongly modified the effect of greater absolute and relative fat mass on insulin and C-peptide levels as well as HOMA-IR in young adulthood, which is consistent with previous studies in full-term 20-year-old subjects [5]. We also found an interaction effect between lower birthweight SDS and greater adult height SDS on insulin level and HOMA-IR, but this probably reflects the effect of greater absolute fat mass (which is closely related to height). The interaction between lower birthweight SDS and greater adult relative fat mass (which is independent of height) on the parameters of insulin resistance suggests an effect of adult fat accumulation rather than of height.

Conclusions and implications

In conclusion, our study in a relatively large cohort of men and women born very preterm showed that rapid infancy weight gain until 3 months predicted higher insulin levels at age 19 years, but the association was weak. Adult fat accumulation strongly predicted higher insulin and C-peptide levels as well as higher HOMA-IR at age 19 years. The effect of adult fat accumulation on these parameters of insulin resistance was dependent on its interaction with birthweight SDS.

A previous study in the same cohort showed that rapid infancy weight gain was a strong predictor of adult fat accumulation [16], whereas this study showed only a weak effect of rapid infancy weight gain until 3 months on insulin level (and no effect on C-peptide level and HOMA-IR) in young adulthood. At present, it is unclear whether interventions aimed at discouraging infancy weight gain would improve adult body composition and reduce the chance of developing type 2 diabetes. However, recent evidence suggests that rapid infancy weight gain of very preterm infants is beneficial for several neurodevelopmental outcomes [37, 38], making intervention (i.e. undernutrition) hard to justify.

Recently, it was found that the survivors of very preterm birth are already more insulin resistant at the age of 7 years [7]. In line with these observations, we found that HOMA-

IR (which normally approximates to 1 in young non-obese persons, if glucose is measured in mmol/l and insulin in mU/l [17]) was relatively high in our study population. Also, we found that our subjects had already some centralisation of fat distribution compared with population references. As there is strong tracking of obesity from childhood to young adulthood [39], we would like to call upon paediatricians and primary healthcare workers (1) to be alert to fat accumulation during childhood in the follow-up of very preterm subjects, especially of those born SGA, and (2) to intervene, even though it has not yet been tested whether weight reduction in very preterm subjects can reverse insulin resistance. The question of whether the survivors of very preterm birth, and especially those born SGA who subsequently become overweight, have a premature onset of type 2 diabetes remains very interesting and should be addressed.

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Appendix

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